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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/489,394	01/21/00	HSEI V	P1085R6

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EXAMINER	
HELMS, L	
ART UNIT	**PAPER NUMBER**
1642	6

DATE MAILED: 08/22/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/489,394	Hsei et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-37* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-37* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. Claims 1-37 are under examination. Claims 38-123 have been canceled.

Drawings

2. The drawings are objected to because the y-axis is missing on Figures 34A-D, 39, 40, 50A-B, 55A-C, 58A-B. Correction is required.

3. The drawings are considered to be informal because they fail to comply with 37 CFR 1.84(a)(1) which requires black and white drawings using India ink or its equivalent.

Photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) or (b)(1) is granted permitting their use as formal drawings. In the event applicant wishes to use the drawings currently on file as formal drawings, a petition must be filed for acceptance of the photographs or color drawings as formal drawings. Any such petition must be accompanied by the appropriate fee as set forth in 37 CFR 1.17(I), three sets of drawings or photographs, as appropriate, and, if filed under the provisions of 37 CFR 1.84(a)(2), an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Specification

4. The disclosure is objected to because of the following informalities:

a. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

b. The ATCC address on page 229, lines 12-13, for example, should be updated to 10801 University Boulevard, Manassas, VA 20110-2209.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-30 are indefinite for reciting "apparent size of the conjugate is at least about" or "apparent size of the antibody fragment" for the exact meaning of the phrase is not clear. It is not clear what is meant by apparent size and how the apparent size is determined. In consideration of the discrepancies in the art between protein molecular weights when determined by different methods, whenever a molecular weight is recited to characterize a protein the claim should include not only the method by which it was determined, i.e., whether by sodium dodecyl sulphate polyacrylamide gel electrophoresis, gel filtration, or some other method, but also whether the determination was made under denaturing or non-denaturing conditions.

b. Claim 14 is indefinite for reciting 'derived from a parental antibody" for the phrase is not clear. The term "derived" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the antibodies are to be derived from the parent to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derived" antibody is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized meaning for the phrase

and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claim is broadly drawn to any antibody fragment, derived from a parent antibody, linked to a nonproteinaceous polymer through a cysteine residue wherein in the parent antibody the heavy and light chains are linked by a disulfide bond and in the antibody fragment the

cysteine in the heavy or light chain is substituted for any amino acid and the cysteine in the opposite chain is covalently linked to a nonproteinaceous polymer molecule.

c. The specification teaches a general method for covalent attachment of a nonproteinaceous polymer to a cysteine residue, however, the specification does not enable the production of a functional antigen binding fragment as broadly claimed. The specification does not enable the replacement of the cysteine residue with any amino acid. One skilled in the art would conclude that not every amino acid, especially those that have bulky side chains, would be tolerated and result in proper folding and packing of the heavy and light chains in the absent of the disulfide bond in the antibody. In addition, the specification fails to teach an example where the disulfide bond linking the cysteine residues in the light or heavy chain is substituted for an amino acid and the cysteine is covalently coupled to a nonproteinaceous polymer that results in a functional antibody. Moreover, As evidenced by Winter (EP 0239400, 9/30/87) Figure 1, it is not clear which disulfide bond connecting the heavy and light chains can be used as claimed and obtain a functional antibody. Figure 1 in Winter illustrates three disulfide bonds connecting the heavy and light chains and as such one skilled in the art would conclude that covalent attachment of a nonproteinaceous polymer at a site away from the hinge region would result in altered packing of the heavy and light chains and thus would not produce an antigen binding fragment. Thus, undue experimentation would be require to make and use the instantly claimed antibody fragments.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 8, 10, 15, 18, 19, 21, 24, 25, and 30-35 of copending Application No. 09/234182. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the 09/234182 case are broader than those encompasses by the conjugates of the instant application. The claims in 09/234182 are directed to a conjugate of an antibody and a non-proteinaceous polymer which is broader than the antibody conjugates of the instant application. It would have been obvious to use any of the antibodies in the instant application for conjugation to a non-proteinaceous polymer. Therefore, the two sets of claims would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was made.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 and 28-31 of copending Application No. 09/355014. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the 09/355014 case are broader than those encompasses by the conjugates of the instant application. The claims in 09/355014 are directed to a conjugate of an antibody and a non-proteinaceous polymer which is broader than the antibody conjugates of the instant application. It would have been obvious to use any of the antibodies in the instant application for conjugation to a non-proteinaceous polymer. Therefore, the two sets of claims would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was made.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 1-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of copending Application No. 09/012116. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the 09/012116 case are broader than

those encompasses by the conjugates of the instant application. The claims in 09/012116 are directed to a conjugate of an antibody and a polymer which is broader than the antibody conjugates to non-proteinaceous polymers of the instant application. It would have been obvious to use any of the antibodies in the instant application for conjugation to a non-proteinaceous polymer. Therefore, the two sets of claims would have been prima facie obvious in view of each other to one of ordinary skill in the art at the time the invention was made.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-13, 15-16, 18-24, 26-33, 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faanes et al (U.S. Patent 5,695,760, filed 4/24/95).

a. The claims are summarized as a conjugate consisting of one or more antibody fragments covalently attached to one or more PEG molecules of molecular weight of at least about 20, 30, and 40kD and wherein the PEG is single chain or branched, wherein the apparent size of the conjugate is at least about 500, 800, 1400, and 1800 kD and wherein the antigen binding site binds human CD18, and wherein the apparent size of the conjugate is at least about 8, 15, and 25 fold greater than the apparent size of the antibody fragment, wherein the antibody fragment is Fab or F(ab')2, further embodiments are the antibody fragment is covalently attached to no more than about 10, 5, 2, or 1 polymer molecules and the antibody fragment is humanized and compositions which are sterile.

b. Faanes et al teach the methods and modifications of antibodies specifically the anti-ICAM-1 antibody with attachment of PEG molecules to the antigen binding fragments. Faanes

et al teach the anti-CD18 antibody (see column 7, lines 50-55) and humanization (column 14, line 40), fragments of the antibody (Fab and F(ab')2) (see column 10, lines 12-13), derivatives of PEG (column 12, lines 19-28), antibodies with biological excipient (column 19, lines 49-57) which are sterile (column 20, line 20), and the antibodies can be modified to contain about 2-15 molecules of PEG (column 6, lines 21-24) with PEG 5 kD to higher molecular weight PEGs (column 14, lines 9-10) . Faanes et al also teach a method for separating fragments of antibodies from PEG-modified fragments (column 13-14) The method can separate PEG-modified antibody fragments with 1, 2, 3, etc, PEG molecules (column 18, lines 19-34). Faanes et al also teach the determination of the apparent molecular weight of the conjugates using the Stokes radius (column 19, lines 35-41) and teaches an antibody which was modified with PEG has a molecular weight of 540 kD (column 19, lines 35-41).

c. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a conjugate consisting of an antigen binding fragment of anti-human CD18 and PEG molecules attached to the antibody at various amounts with various molecular weight PEG molecules as taught by Faanes et al.

d. One of ordinary skill in the art would have been motivated to have produced a conjugate consisting of an antigen binding fragment of anti-human CD18 and PEG molecules attached to the antibody at various amounts with various molecular weight PEG molecules as taught by Faanes et al because Faanes et al teach that both the anti-ICAM-1 and anti-CD18 antibodies have been used to intervene in the cellular adhesion process (column 7, lines 50-54).

In addition, one of ordinary skill in the art would have been motivated to have produced a conjugate consisting of an antigen binding fragment of anti-human CD18 and PEG molecules attached to the antibody at various amounts with various molecular weight PEG molecules as taught by Faanes et al because Faanes et al teach the method for derivitization of the antibody with PEG can be optimized and the chromatographic method can be used to obtain antibodies modified with various amounts of PEG which increases the stokes radius of the antibody and the PEG-modified antibody species may differ in their in vivo serum half-lives (column 7, lines 6-8). One of ordinary skill in the art would know that one could use the method of Faanes et al and obtain various antibodies with various molecular weight PEG molecules and derivatives attached at various amounts to obtain the desired characteristics of the conjugates.

e. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success to have produced a conjugate consisting of an antigen binding fragment of anti-human CD18 and PEG molecules attached to the antibody at various amounts with various molecular weight PEG molecules as taught by Faanes et al because Faanes et al teach that as a consequence of the modification of the antibody, the conjugates exhibit improved therapeutic characteristics (column 1, lines 10-14).

f. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. Claims 1-13, 15-33, 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faanes et al (U.S. Patent 5,695,760, filed 4/24/95) and further in view of Zapata et al (FASEB J. 9:A1476, 1995).

a. Claims 1-13, 15-16, 18-24, 26-33, and 36-37 have been described supra. Claims 17 and 25 recite wherein the nonproteinaceous polymer or PEG is covalently attached to the hinge region of the antibody fragment.

b. Faanes et al has been described supra. Faanes et al does not teach attachment of PEG to the hinge region of the antibody fragment. This deficiency is made up for in the teachings of Zapata et al.

c. Zapata et al teach covalent attachment of MePEG to an antibody fragment of Fab' or F(ab')2 through the single free thiol in the hinge region. The fragments are a humanized antibody.

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a antigen binding fragment with PEG attached in the hinge region as taught by Zapata et al and producing a conjugate with the claimed characteristics as taught by Faanes et al.

e. One of ordinary skill in the art would have been motivated to have produced an antigen binding fragment with PEG attached in the hinge region as taught by Zapata et al and producing a conjugate with the claimed characteristics as taught by Faanes et al because Zapata et al teach the "humanized anti-CD18 Fab' fragment, which contains a single free thiol, was

expressed in E. Coli and recovered in high yield". In addition, Zapata et al teach "modification of the anti-CD18 Fab' with either size of MePEG maleimide did not alter the ability of this molecule to bind antigen". In addition, Zapata et al teach that the pharmacokinetic data show that the MePEG-Fab' species had reduced clearance as compared to the native Fab'.

f. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Zapata et al teach MePEG was used to selectively modify the single free thiol of the Fab' polypeptide in a rapid and efficient reaction.".

g. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

17. Claims 1 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faanes et al (U.S. Patent 5,695,760, filed 4/24/95) and further in view of Harlow et al (Antibodies A Laboratory Manual, Cold Spring Harbor Laboratories, pp 324-339, 1988).

a. Claim 1 has been described supra. Claims 34 and 35 recite the conjugate incorporates one or more radiolabels.

b. Faanes et al has been described supra. Fannes et al does not teach a conjugate comprising a radiolabel. This deficiency is made up for in the teachings of Harlow et al.

c. Harlow et al teach radiolabeling of antibodies.

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an anti-CD18 antibody conjugate with PEG attached as taught by Faanes et al and radiolabel the antibody as taught by Harlow et al.

e. One of ordinary skill in the art would have been motivated to have produced an anti-CD18 antibody conjugate with PEG attached as taught by Faanes et al and radiolabel the antibody as taught by Harlow et al because Faanes et al teach the in vivo serum half-life of the PEG-conjugated antibodies are greater than the serum half-life of the non PEG-conjugated antibodies. In addition, one of ordinary skill in the art would have been motivated to have produced an anti-CD18 antibody conjugate with PEG attached as taught by Faanes et al and radiolabel the antibody as taught by Harlow et al because Harlow et al teach "125I is normally used for most immunochemical analysis." (See page 324). Further Harlow et al teaches "The decay of 125I yields low-energy gamma and X-ray radiation and, therefore, is easy to detect." (See page 324).

f. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success to have produced an anti-CD18 antibody conjugate with PEG attached as taught by Faanes et al and radiolabel the antibody as taught by Harlow et al because Harlow et al teach "Iodination of antibodies and other proteins is straightforward and effective method of labeling." (See page 324).

g. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

18. No Claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Sheela J. Huff

SHEELA HUFF
PRIMARY EXAMINER

Respectfully,

Larry R. Helms Ph.D.